510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

k043202

B. Purpose for Submission:

Clearance of new reagent format (to lengthen stability claim) and addition of a new matrix (plasma)

C. Measurand:

Creatine kinase

D. Type of Test:

Quantitative enzymatic colorimetric assay

E. Applicant:

Olympus America, Inc.

F. Proprietary and Established Names:

Olympus Creatine Kinase Reagent

G. Regulatory Information:

1. Regulation section:
   21 CFR §862.1215, Creatine phosphokinase/creatine kinase or isoenzymes test system

2. Classification:
   Class II

3. Product code:
   CGS - NAD reduction/NADH oxidation, CPK or isoenzymes

4. Panel:
   Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

   The Olympus Creatine Kinase reagent is intended for use in Olympus automated clinical chemistry analyzers for the quantitative determination of creatine kinase activity in human serum and plasma.

   Measurements of creatine kinase are used in the diagnosis and treatment of myocardial infarction and muscle diseases such as progressive, Duchenne-type muscular dystrophy.

2. Indication(s) for use:

   See intended use above

3. Special conditions for use statement(s):

   For professional use only

4. Special instrument requirements:

   Olympus AU400/AU400e, AU600/AU640/AU640e, or AU2700/AU5400 analyzers

I. Device Description:

The Olympus Creatine Kinase reagent consists of 3 ready-to-use liquid reagents to be used on the Olympus family of analyzers. The reagents contain buffers, preservatives, stabilizers, and the reactive compounds and enzymes listed in Test Principle section below.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Olympus Creatine Kinase Reagent

2. Predicate 510(k) number(s):

   k994189

3. Comparison with predicate:

   This device is a second generation device with additional matrix claims and slight modifications to the way reagents are supplied.

Similarities		
Item	Device	Predicate
Reagents	Identical in final reaction mixture	Identical in final reaction mixture
Open vial stability	30 days	30 days

Differences		
Item	Device	Predicate
Matrix	Serum and plasma	serum
Reagent format	3 liquid reagents	2 liquid reagents

K. Standard/Guidance Document Referenced (if applicable):

NCCLS Guideline EP5-A – Evaluation of Precision Performance of Clinical Chemistry Devices
NCCLS Guideline EP6-P – Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach
NCCLS Guideline EP7-P – Interference testing in Clinical Chemistry
NCCLS Guideline EP9-A – Method comparison and Bias Estimation using Patient Samples

L. Test Principle:

The Olympus creatine kinase reagent measures creatine kinase activity in the sample via the following mechanism:

$$\text{Creatine phosphate} + \text{ADP} \xrightarrow{\text{Creatine kinase (from sample)}} \text{creatine} + \text{ATP}$$

$$\text{ATP} + \text{glucose} \xrightarrow{\text{Hexokinase, } Mg^{2+}} \text{ADP} + \text{glucose-6-phosphate (G-6-P)}$$

$$\text{G-6-P} + NADP^{+} \xrightarrow{\text{G-6-P-dehydrogenase}} \text{6-phosphogluconate} + NADPH + H^{+}$$

The rate of increase in absorbance at 340/660 nm from NADPH production is directly proportional to the activity of creatine kinase in the sample.

M. Performance Characteristics (if/when applicable):

1. <u>Analytical performance:</u>
   a. Precision/Reproducibility:

Assay imprecision was evaluated by testing 3 serum-based control pools in duplicate twice a day for 20 days (total n per sample = 80) on each of three analyzer systems. Results are summarized below (units = U/L):

AU400:

	Within Run		Total	
Mean	**SD**	**%CV**	**SD**	**%CV**
101.91	2.08	2.04 %	5.55	5.44 %
278.03	2.63	0.95 %	8.89	3.20 %
836.08	5.11	0.61 %	29.60	3.54 %

AU600/AU640e:

	Within Run		Total	
Mean	**SD**	**%CV**	**SD**	**%CV**
104.16	2.22	2.13 %	5.46	5.25 %
284.10	3.32	1.17 %	9.93	3.50 %
853.97	3.61	0.42 %	30.06	3.52 %

AU2700/AU5400:

	Within Run		Total	
Mean	**SD**	**%CV**	**SD**	**%CV**
99.00	2.35	2.37 %	4.51	4.55 %
270.16	2.70	1.00 %	8.64	3.20 %
810.43	5.22	0.64 %	26.59	3.28 %

A second set of precision data was generated using 4 samples for inclusion in the package insert. Samples were tested in duplicate twice a day for 20 days (total n per sample = 80) on each of three analyzer systems. Results are summarized below (units = U/L):

AU400/AU400e:

	Within run		Total	
Mean (U/L)	**SD**	**CV%**	**SD**	**CV%**
115	0.68	0.60	1.18	1.00
137	0.73	0.50	1.65	1.20
455	1.88	0.40	4.38	1.00
510	2.02	0.40	3.92	0.80

AU600/AU640/AU640e:

	Within run		Total	
Mean (U/L)	**SD**	**CV%**	**SD**	**CV%**
117	1.22	1.00	1.77	1.50
135	2.04	1.50	3.83	2.80
452	4.85	1.10	11.47	2.50
498	5.44	1.10	9.94	2.00

AU2700/AU5400:

Mean (U/L)	Within run		Total	
	SD	CV%	SD	CV%
118	0.99	0.80	2.34	2.00
138	1.30	0.90	1.93	1.40
465	3.07	0.70	5.37	1.20
500	4.46	0.90	9.54	1.90

b. Linearity/assay reportable range:

The linearity of the assay was evaluated by testing a commercially available linearity set that covers the useable range. Each level was assayed in quadruplicate, and the mean results were plotted against the expected results. The regression statistics for testing on each analyzer are as follows:

AU400: slope = 0.977; intercept = -0.496
AU640: slope = 0.988; intercept = -0.816
AU2700: slope = 0.933; intercept = -1.2305

The data support the package insert claim that the assay is linear from 10-2000 U/L.

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

No traceability was provided.

On-board stability of the reagents was evaluated. Protocols and acceptance criteria were reviewed and found to be acceptable. The studies support an on-board stability claim of 30 days.

d. Detection limit:

The analytical sensitivity of the assay, calculated adding three standard deviations to the mean of 20 replicates of an analyte-free sample, was determined to be 2-3 U/L, which is below the stated claim of 10 U/L, +/- 5 U/L.

The sponsor states in the package insert that the typical change in absorbance per minute for 1 U/L of CK is 0.12 mAbsorbance for all members of the Olympus family of chemistry analyzers.

e. Analytical specificity:

Potential interferences were evaluated by testing samples spiked with increasing concentrations of bilirubin (AU640), hemoglobin (AU400), or Intralipid (AU2700- to test for interference by lipemia). Results are summarized below:

Bilirubin added (mg/dL)	% Recovery
0	100.0
4	100.8
8	101.6
12	101.4
16	100.2
20	102.2
24	103.6
28	101.9
32	103.7
36	102.1
40	101.8

Hemolysate added (mg/dL)	% Recovery
0	100.0
50	101.5
100	103.2
150	104.0
200	103.9
250	104.5
300	103.5
350	105.3
400	104.8
450	105.6
500	105.8

Intralipid added (mg/dL)	% Recovery
0	100.0
100	98.7
200	98.8
300	97.8
400	98.8
500	98.4
600	98.5
700	97.6
800	97.7
900	99.1
1000	98.3

f. Assay cut-off:
Not applicable

2. Comparison studies:
   a. *Method comparison with predicate device:*

Both serum and plasma samples were run using both the predicate reagent (current version of the reagent) and the new reagent (device). Least squares regression statistics are summarized below :

Serum : Device = 0.992(Predicate) + 0.026
Correlation coefficient = 1.000
Range = 21.73 – 1903.13

Plasma : Device = 0.990(Predicate) + 0.872
Correlation coefficient = 1.000
Range = 18.00 – 1967.00

Samples run with the AU640 analyzer (Validated in separate experiments versus the predicate - see above) was compared to the same samples run on the AU400 and AU2700/AU5400 analyzers. Least squares regression statistics are summarized below :

AU400 : AU400 = 1.040(AU640) – 2.089
Correlation coefficient = 0.999
Range = 17.70 – 1879.78

AU2700/AU5400 : AU2700/AU5400 = 0.999(AU640) – 1.763
Correlation coefficient = 1.000
Range = 17.70 – 1879.78

   b. *Matrix comparison:*

The sponsor performed accuracy testing on both serum and plasma samples (see above).

3. Clinical studies:
   a. *Clinical Sensitivity:*
   Not applicable

   b. *Clinical specificity**:***
   Not applicable

   c. Other clinical supportive data (when a. and b. are not applicable):
   Not applicable

4. Clinical cut-off**:**
   Not applicable

5. Expected values/Reference range:

   This information is the same as for the predicate device (k994189). The expected values in an adult population are 30-223 U/L creatine kinase. The applicant states that this range is based on data collected from 200 blood donors in North Texas.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.